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Commentary

The emergence of antihistamines as unexpected allies in our fight against acute myeloid leukaemia

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Acute myelogenous leukaemia (AML) is a heterogeneous group of hematopoietic malignancies that are characterized by unique molecular, cellular and clinical features. Despite these biological heterogeneities, AML is not easy to cure [1]. In the modern treatment era, improved outcomes have resulted from risk-adjusted therapies that often call for bone marrow transplantation, or the testing of novel agents that are integrated into dose-intensified treatment protocols. Neither are effective in the absence of good supportive care. The repertoire of supportive care medications that are used in the treatment of AML is quite extensive, but broadly includes the use of antihistamines to treat allergic reactions to medications, blood products, or other immune-mediated events [2]. As a class of H1 receptor antagonists, antihistamines have not been utilized as cytotoxic therapies in the treatment of AML, but new evidence might change that way of thinking.

Using an *in silico* screening assay to assess the cytotoxic effects of FDA-approved drugs for the treatment of AML, Cornet-Masana and colleagues [3] identified a subset of antihistamines with distinct physicochemical properties that selectively killed AML cell lines and primary patient samples. Starting with gene expression profiling experiments involving an MLL-AF9 induced AML model, the authors found HRH1 inverse agonists had properties that reversed the transformation gene signature. The selected antihistamines were next found to significantly reduce the proliferation rate in a variety of AML cell lines. Upon closer evaluation, the subset of antihistamines exerted their killing effects not through receptor-mediated signaling, but through the simultaneous disruption of lysosomes and mitochondria. These diffusion-dependent effects subsequently interfered with energy-dependent mitotic events. Importantly, the induction of apoptosis and autophagy was independent of the AML genomic landscape of molecular lesions, and does not appear to depend upon the disruption of receptor-mediated signaling events.

Because the acute leukaemias are hosted by complex cell populations, sometimes divided by sanctuary sites, cytotoxicity has a strong contextual component. For instance, asparagine is not one of the nine essential amino acids that humans require for survival. But lymphoid progenitors, including acute lymphoblastic leukaemic (ALL) blasts are unable to manufacture asparagine for use in nucleosynthesis, and are therefore completely dependent upon serum concentrations for survival. When serum concentrations are reduced to nearly undetectably levels by the exogenous administration of asparaginase, the lymphoblasts subsequently die [4]. Similarly, testicular and central nervous compartments are protected by a testes- and blood-brain barriers, respectively, which block the diffusion of many cytotoxic compounds that are commonly used to treat AML and ALL. For these reasons, successful treatment strategies for all of the acute leukaemias must include compounds that cross sanctuary sites either through diffusion or, in the case of the blood-brain-barrier, directly delivered with intrathecal administration [5]. As a result of extensive pre-clinical and clinical testing, H1 antagonists can be dosed to achieve therapeutic serum concentrations. Repurposing these agents to passively disrupt lysosomal and mitochondrial function introduces the possibility of benefit in the treatment of AML. In the model provided by Cornet-Masana et al., HRH1 inverse agonists might be utilized to safely target malignantly transformed myeloblasts in blood, marrow and sanctuary sites as chemo-sensitizing agents, regardless of compartmental context.

Leukaemia therapies targeted against specific molecular lesions and receptor-mediated signaling events have been an exciting chapter in the 21st century [6]. But as with the case of all novel therapies, new drugs are often associated with unexpected adverse events, some of which may occur much later in life. The class of FDA-approved drugs that are described in the article by Cornet-Masan et al. would not be expected to have serious late effects, because we already know how they behave. As to whether these agents, originally developed for supportive care purposes, can be harnessed as chemo-sensitizing agents remains an untold story. We will only know the answer in the context of a well-designed, prospective clinical trial that utilizes all of our best tools to treat AML, because the assurance of cure is still a long way off.

Declaration of Competing Interest

The author declares no conflicts of interest.

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